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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/582,304	04/20/2007	Naoki Kimura	14875-166US1 CI-A0323P-US	4817

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EXAMINER	
GUSSOW, ANNE	

ART UNIT	PAPER NUMBER
1643	

NOTIFICATION DATE	DELIVERY MODE
12/09/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

Office Action Summary	Application No.	Applicant(s)	
	10/582,304	KIMURA ET AL.	
	Examiner	Art Unit	
	ANNE M. GUSSOW	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 July 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,17-24 and 29-46* is/are pending in the application.

4a) Of the above claim(s) *17-21,29-31 and 35-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 22-24* is/are rejected.

7)☒ Claim(s) *8-10 and 32-34* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The office action mailed October 14, 2010 is hereby **VACATED** in view of the new grounds of rejection below.

2. Claim 4 has been amended.

Claims 11-16 and 25-28 have been cancelled.

Claims 17-21, 29-31, and 35-46 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on December 16, 2008.

3. Claims 1-10, 22-24, and 32-34 are under examination.

4. The following office action contains NEW GROUNDS of Rejection.

Information Disclosure Statement

5. The information disclosure statements (IDS) submitted on July 26, 2010 and September 21, 2010 were filed after the mailing date of the non-final office action on March 24, 2010. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements have been considered by the examiner and an initialed copy of the IDS was mailed to applicant on October 14, 2010.

Applicant is kindly asked to request an additionally copy of these documents should another copy be required.

Rejections Withdrawn

6. The rejection of claims 1-10, 22-24, and 32-34 under 35 U.S.C. 103(a) as being obvious over Ozaki, et al in view of Beresford, et al. as evidenced by the specification is withdrawn in view of applicant's arguments regarding the availability of the 2D7 antibody.

NEW GROUNDS of Rejection

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1 and 22-24 are rejected under 35 U.S.C. 102(b) as being anticipated by Tawara, et al. (WO 03/03358, published April 24, 2003, English equivalent US PAT 7,262,278, as cited on the IDS filed April 1, 2009).

The claims recite an antibody comprising two heavy chain variable regions and two light chain variable regions, wherein the antibody is a single chain polypeptide having a binding activity against human leukocyte antigen (HLA). A pharmaceutical composition comprising the antibody of claim 1 as an active ingredient, wherein the

antibody has cell death inducing activity against B cells or T cells, wherein the B cells or T cells are activated B cells or activated T cells.

Tawara, et al. teach single chain antibodies that bind to human leukocyte antigen (HLA). Tawara, et al. teach the antibodies may be sc(Fv)2 formats. Tawara, et al. teach the antibodies in pharmaceutical compositions. The limitations of claims 23 and 24 are inherent properties of an antibody. Since the antibody would bind to an antigen on a B cell or T cell, the antibody would necessarily have a cell death inducing activity against those cells. Since the claims do not define the specific antibody that binds to HLA, and Tawara, et al. teach single chain antibodies that bind to human leukocyte antigen in a pharmaceutical composition, all the limitations of the claims have been met.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 1-4, 7, and 22-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tawara, et al. (WO 03/03358, published April 24, 2003, English equivalent US PAT 7,262,278) in view of Mezes, et al. (US PAT 5,877,291 issued March 2, 1999, as cited on the IDS filed May 31, 2007).

Claims 1 and 22-24 have been described supra. Claims 2-4 and 7 recite the antibody of claim 1, wherein the two heavy chain variable regions and two light chain variable regions are arranged in the order of heavy chain variable region, light chain variable region, heavy chain variable region, and light chain variable region, starting from the N terminus of the single chain polypeptide, further comprising linkers between the variable regions, wherein each of the linkers comprises 15 amino acids, wherein the antibody is sc(Fv)2.

Tawara, et al. has been described supra. Tawara, et al. suggests that it would be useful to have a “polymer” of an scFv that binds to HLA-DR (an MHC II antigen)(e.g.

see column 7, lines 58-67). Tawara et al does not exemplify or prophetically teach how one would construct such a multivalent single chain antibody against HLA-DR. These deficiencies are made up for in the teachings of Mezes, et al.

Mezes, et al. teach methods for constructing multivalent single chain antibodies (e.g. Abstract, Working Examples). Mezes, et al. teach that an advantage of sc(Fv)2 over sc(Fv) is that the increased number of binding sites (i.e. variable domains) can increase binding affinity of the antibody for the desired target and/or allow for the incorporation of additional target-binding moieties into the antibody (e.g. for antibody capture, etc.; e.g. column 3, lines 16-30). In addition, Mezes, et al. teach the arrangement of V_H & V_L domains recited in the instant claims (e.g. V_H-L-V_L-L-V_H-L-V_L; e.g. see column 3, lines 48-62; column 7, lines 62-67). Linker size is discussed in column 5 of the patent, with a preferred linker of 25 amino acids specifically taught (e.g. column 5, lines 19-41).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the scFv antibody taught by Tawara, et al. to form a V_H-L-V_L-L-V_H-L-V_L-type sc(Fv)2 antibody as taught by Mezes, et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have modified the scFv antibody taught by Tawara, et al. to form a V_H-L-V_L-L-V_H-L-V_L-type sc(Fv)2 antibody as taught by Mezes, et al. because Tawara, et al. teach such “polymeric” scFv antibodies against HLA-DR are desirable and because Mezes, et al. teach that the construction of multivalent sc(Fv)2 single chain antibodies is within the skill of the art. One would have been motivated to

do so in order to receive the expected benefit of obtaining an antibody having enhanced binding to the desired target relative to the monovalent scFv as well as other potential benefits as suggested by Mezes, et al. Absent any evidence to the contrary, there would have been a reasonable expectation of success in constructing an anti-HLA-DR sc(Fv)2 utilizing the combined teachings of the two cited references. Thus, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to have modified the scFv antibody taught by Tawara, et al. to form a V_H-L-V_L-L-V_H-L-V_L-type sc(Fv)2 antibody in view of Mezes, et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made as evidenced by the references.

13. Claims 1-7 and 22-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Isobe, et al. (US PAT 5,223,241, issued June 29, 1993) in view of Mezes, et al. (US PAT 5,877,291, issued March 2, 1999, as cited on the IDS filed May 31, 2007) as evidenced by Morganelli, et al. (US PAT 5,077,216, issued December 31, 1991).

Claims 1-4, 7, and 22-24 have been described supra. Claims 5 and 6 recite the antibody of claim 1, wherein HLA is HLA class I, wherein HLA class I is HLA-A.

Isobe, et al. teach methods of detecting rejection of an allograft in a mammal comprising administering to the mammal an effective amount of a composition comprising at least one monospecific immunoglobulin molecule or fragment thereof diagnostically conjugated to a detectable label, where the immunoglobulin is directed

against an MHC antigen and where one detects rejection of the allograft by detecting the presence of the labeled immunoglobulin or fragment. In particular, Isobe, et al. teaches that the antibody used can be the commercially-available mAb W6/32 (e.g. claims 1-6).

Morganelli et al characterize mAb W6/32 as being "an IgG2 which binds to a framework determinant on HLA-A and –B antigens."

Mezes, et al. is described supra. Mezes teaches additional advantages for their sc(Fv)2 multivalent antibody fragments, including increased capillary permeability, more rapid biodistribution pharmacokinetics, more rapidly reaching their target *in vivo* and more rapid clearing from the body (e.g. column 6, lines 61-67 ; Working Example 4 at column 18). In addition, the Isobe patent teaches that the sc(Fv)2 of their invention can be conjugated with appropriate imaging agents via methods known in the art (e.g. column 7, lines 1-14).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the W6/32 mAb taught by Isobe, et al. to the sc(Fv)2 structure as taught by Mezes, et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have modified the W6/32 mAb taught by Isobe, et al. to the sc(Fv)2 structure as taught by Mezes, et al. because anti-HLA-A antibodies and methods of their use were well known in the art at the time of the instant invention. For many of these HLA-A-specific antibodies, it would have been obvious to modify the

known antibody to incorporate the sc(Fv)2 structure taught by Mezes, et al. in order to obtain the benefits suggested by Mezes for such multivalent single-chain antibodies.

Further, Isobe, et al. teach that the anti-HLA-A mAb is useful in their diagnostic methods and Mezes, et al. teach it is within the skill of the art to modify antibodies having known affinities to obtain polymeric single-chain antibodies (i.e. sc(Fv)2) that retain their original binding specificity. One would have been motivated to do so in order to attain the advantages taught by Mezes, et al. for such sc(Fv)2 molecules. Absent any evidence to the contrary, there would have been a reasonable expectation of success in utilizing the combined teachings of the two cited reference to obtain and use an sc(Fv)2 having specificity for HLA-A. Thus, it would have been obvious to have modified the W6/32 mAb taught by Isobe, et al. to the sc(Fv)2 structure in view of Mezes, et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made as evidenced by the references.

Conclusion

14. Claims 1-7 and 22-24 are rejected.

Claims 8-10 and 32-34 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANNE M. GUSSOW whose telephone number is (571)272-6047. The examiner can normally be reached on Monday - Friday 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Misook Yu can be reached on (571) 272-0839. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anne M. Gussow
December 6, 2010

/Anne M. Gussow/
Primary Examiner, Art Unit 1643